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In- or In(I)-Employed Diastereoselective Reformatsky-Type Reactions with Ketones: ^{1}H NMR Investigations on the Active Species

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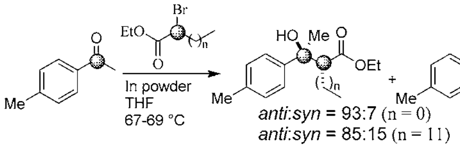
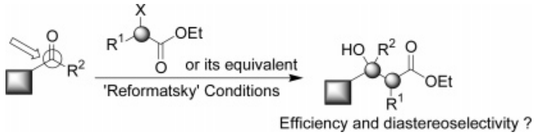
ABSTRACT



An efficient In- or In(I)-based stereoselective C−C bond formation is reported; the diastereoselective Reformatsky-type reactions of ketones. The predominant formations of *anti* isomers, confirmed by the X-ray structure analyses of ester derivatives of respective alcohols 9a$_1$ and 13a$_1$, conclusively revealed the stereochemistry of the reaction path. ^{1}H NMR investigations revealed the formation of two types of α-metalated transient species from α-halo esters with In or In(I) halides.

Stereoselective carbon−carbon bond formation is the foundation for synthetic organic chemistry, and organometallic reactions are among the superior processes. A classic procedure in this respect is the Reformatsky-type reaction.[1] Many processes have been developed using zinc.[2] For very high efficiency, new methods were developed, e.g., Rieke-Zn,[3a] Zn−Cu couple,[3b] and Zn/Ag-graphite,[3c] utilizing other metals such as Cd,[3d] Ni,[3e] Ce,[3f] Mg,[3g,h] and indium;[4] however, some of these reagents must be freshly prepared.[3] Despite these developments and considering the applicability and versatility of the Reformatsky-type reaction, an enduring problem remains to be explored, that is, an efficient diastereoselective addition of the branched α-halo ester derivatives to ketones. In view of the stereochemical synthetic point, this process would produce two stereogenic centers; however, there have been a few examples with only moderate diastereoselectivity. This is probably because the conditions to achieve the additions to ketones are too severe to control the stereoselectivity in contrast to the facile additions to aldehydes (Scheme 1). In addition, the difference in the rigid steric demand between the two substituents on the carbonyl carbon importantly decides the degree of stereoselection. This difference is much lower in the case of ketones than aldehydes. In fact, a survey of the existing examples on the

Scheme 1



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[1] Reformatsky, S. *Chem. Ber.* **1887**, *20*, 1210.

[2] (a) Fürstner. A. *Synthesis* **1989**, 571. (b) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2, p 277.

[3] (a) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452. (b) Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698. (c) Csuk, R.; Fürstner, A.; Weidmann, H. *J. Chem. Soc., Chem Commun.* **1986**, 775. (d) Burkhardt, E.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 416. (e) Inaba, S.-I.; Rieke, R. D. *Tetrahedron Lett.* **1985**, *26*, 155. (f) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. (g) Moriwake, T. *J. Org. Chem.* **1966**, *31*, 983. (h) Borno, A.; Bigley, D. B. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1311. (i) Paresh, J. D.; Shelton, D. R.; Little, R. D. *Org. Lett.* **2003**, *5*, 3615. (j) Shibata, I.; Suwa, T.; Sakakibara, H.; Baba, A. *Org. Lett.* **2002**, *4*, 301 and references therein.

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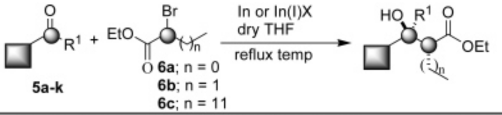
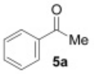
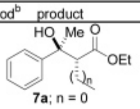
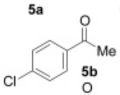
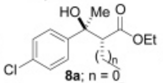
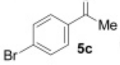
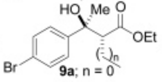
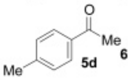
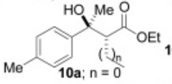
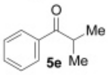
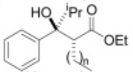
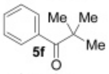
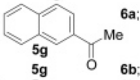
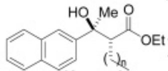
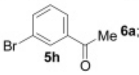
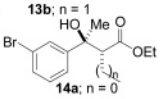
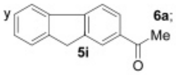
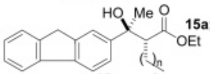
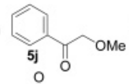
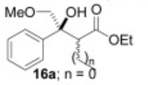
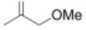
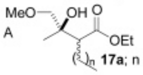
addition of the branched α-halo esters to ketones revealed the difficulty in achieving good diastereoselectivity,[5,6] e.g., Zn dust/I_2 (*anti*/*syn* 3:2),[6] $Et_2Zn/RhCl(PPh_3)_3$ (*anti*/*syn* 1:1),[5a] and low-valent tantalum (ds 17:13).[5b]

Taking an impetus from the recently advancing selective reactions based on indium,[4,7] we envisioned the indium-based diastereoselective Reformatsky-type reactions of ketones. We herein report our investigations on the stereoselective C−C bond formations using In or In(I)X.

The scope and result of the reactions of the branched α-halo ester derivatives such as **6a**−**c** with ketones in the Reformatsky-type condition and the degree of stereoselection would depend on two essential things: (a) a large difference in steric demand between the two substituents on the carbonyl carbon of ketones and (b) the strict conformation of a six-membered cyclic transition state that would result from a transient indium enolate ("*E*" or "*Z*"). In an initial experiment, to a mixture of acetophenone and ethyl 2-bromopropionate in dry THF was added indium metal powder at room temperature, and the resulting mixture was heated to reflux to afford the product **7a**[5,6] in 98% yield with diastereoselectivity of 75:25 (*anti*/*syn*) (Table 1, entry a). We found that dipping the flask containing all the contents in dry THF into a preheated bath for 1 h gave the product with higher selectivity 84:16 (*anti*/*syn*) (entry b). Then we were interested in employing the indium(I) halides for the above stereoselective reaction. Indium(I) bromide is found to be more efficient than indium(I) chloride or indium(I) iodide. Employing indium(I) bromide gave significantly higher diastereoselectivity with very good yield. The generality of this important stereoselective reaction was demonstrated with a variety of ketones as summarized in Table 1. Electron-withdrawing and donating groups slightly altered the diastereoselectivities. The reactions with the α-halo ester derivative **6c** having a long carbon chain length also afforded the products **7c** and **10c** with high diastereoselectivities (entries j, k, and q). Employing other conditions such as ultrasonication/rt, solvents such as MeCN and DMF, or using MeCH(Cl)COOEt or RX/NaI -in DMF/rt systems[4,7] were ineffective. Compared to the existing methods, the indium-based reagents[8] behaved in a distinctive manner with respect to the diastereoselectivity.[9a]

Table 1. Indium-Based Diastereoselective Reformatsky-type Reaction of Ketones **5** with **6a**−**c**[a]



entry	ketone	α-halo ester	In/InX	T/(h)	method[b]	product	yield (%) (*ds*)
a	 **5a**	**6a**; n = 0	In	2.5	B	 **7a**; n = 0	**7a**; 98 (75:25)
b			In	1.0[c]	A		**7a**; 99 (84:16)
c			InCl	8.0	B		**7a**; 99 (76:24)
d			InBr	3.5	B		**7a**; 84 (84:16)
e			InI	9.0	B		**7a**; 67 (68:32)
f			In	1.0	C		NR
g			$InCl_2$	2.0[c]	A		NR
h	**5a**	**6b**; n = 1	In	2.5[c]	A	**7b**; n = 1	**7b**; 99 (79:21)
i	**5a**	**6b**; n = 1	InBr	3.0[c]	A	**7b**; n = 1	**7b**; 87 (82:18)
j[d]	**5a**	**6c**; n = 11	In	8.0[c]	A	**7c**; n = 11	**7c**; 65 (83:17)
k	**5a**	**6c**; n = 11	InBr	7.0[c]	A	**7c**; n = 11	**7c**; 51 (82:18)
l	 **5b**	**6a**; n = 0	In	3.0	B	 **8a**; n = 0	**8a**; 99 (75:25)
m			InBr	3.5	B		**8a**; 90 (84:16)
n	 **5c**	**6a**; n = 0	In	3.0	B	 **9a**; n = 0	**9a**; 86 (75:25)
o	**5c**	**6b**; n = 1	In	2.5[c]	A	**9b**; n = 1	**9b**; 97 (82:18)
p	 **5d**	**6a**; n = 0	In	1.0[c]	A	 **10a**; n = 0	**10a**; 88 (93:7)
q[d]	**5d**	**6c**; n = 11	In	5.5[c]	A	**10c**; n = 11	**10c**; 69 (85:15)
r	 **5e**	**6a**; n = 0	In	70 min[c]	A	 **11a**; n = 0	**11a**; 60 (69:31)
s	 **5f**	**6a**; n = 0	In	70 min[c]	A	**12a**	NR
t	 **5g**	**6a**; n = 0	In	70 min[c]	A	 **13a**; n = 0	**13a**; 98 (85:15)
u			InBr	4 h	B		**13a**; 97 (85:15)
v	**5g**	**6b**; n = 1	In	3.0[c]	A	**13b**; n = 1	**13b**; 90 (80:20)
w	**5g**	**6b**; n = 1	InBr	3.0[c]	A	**13b**; n = 1	**13b**; 94 (82:18)
x	 **5h**	**6a**; n = 0	InBr	3.5	B	 **14a**; n = 0	**14a**; 88 (73:27)
y	 **5i**	**6a**; n = 0	In	1.0[c]	A	 **15a**; n = 0	**15a**; 95 (86:14)
z	**5i**	**6b**; n = 1	In	1.5[c]	A	**15b**; n = 1	**15b**; 91 (80:20)
aa	 **5j**	**6a**; n = 0	In	3.0	B	 **16a**; n = 0	**16a**[e] 90 (82:18)
ab	 **5k**	**6a**; n = 0	InBr	2.0[c]	A	 **17a**; n = 0	**17a**[e]; 81 (77:23)

[a] In all reactions, **5** (1 mmol), **6a**−**c** (1.6−1.8 mmol), In/In(I)X (~1.2 mmol), and dry THF (~2 mL) were used. Ratios of *anti*/*syn* isomers are shown in parentheses. [b] See the Supporting Information for the details of methods A−C.[9c] [c] The contents of the reaction mixture were dipped into a preheated bath at reflux temperature (~66−69 °C). [d] **5a** (1 mmol), **6c** (2 mmol), and indium (2 mmol) were used. [e] Isolated as a mixture of diastereomers.

Stereochemistry. We have isolated both the major and minor isomers in pure form in some cases. The ester derivatives (of alcohols) of major isomers $\mathbf{9a_1}$ and $\mathbf{13a_1}$ were prepared according to the literature method[9b] in the crystalline forms, suitable for the X-ray structure analyses. The stereo-

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(4) For recent reviews, see: (a) Cintas, P. *Synlett* **1995**, 1087. (b) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633. (c) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B.; S. *Tetrahedron* **2004**, *60*, 1959. (d) Chan, T. H.; Li, C.-J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181.

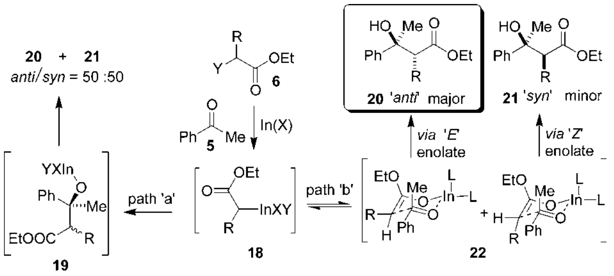
(5) (a) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549 and references therein. (b) Aoyagi, Y.; Tanaka, W.; Ohta, A. *J. Chem. Soc., Chem. Commun.* **1994**, 1225. (c) Delaunay, J.; Orliac-Le Moing, A.; Simonet, J. *Tetrahedron* **1988**, *44*, 7089. (d) Canceill, J.; Basselier, J. J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 1024.

(6) Ross, N. A.; Bartsch, R. A. *J. Org. Chem.* **2003**, *68*, 360 and references therein.

(7) For some recent papers, see: (a) Kumar, S. Kaur, P. *Tetrahedron Lett.* **2004**, *45*, 3413. (b) Loh, T.-P.; Yin, Z.; Song, H.-S.; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 911. (c) Yi, X.-H.; Meng, Y.; Li, C.-J. *J. Chem. Soc., Chem. Commun.* **1998**, 449. (d) Hirashita, T.; Kamei, T.; Satake, M.; Horie, T.; Shimizu, H.; Araki, S. *Org. Biomol. Chem.* **2003**, *1*, 3799. (e) Babu, S. A.; Yasuda, M.; Shibata, I., Baba, A. *Synlett* **2004**, 1223. (f) Paquette, L., A. *Synthesis* **2003**, 765.

(8) For early works dealing with nondiastereoselective Reformatsky-type reactions, see: (a) Chao, L.-C.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253. (b) Nair, V.; Jayan, C. N.; Ros, S. *Tetrahedron* **2001**, *57*, 9453. (c) Araki, S.; Ito, H.; Butsugan, Y. *Synth. Commun.* **1988**, *18*, 453. (d) Araki, S.; Katsumura, N.; Kawasaki, K.-I.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 499. (e) Schick, H.; Ludwig, R.; Schwarz, K.-H.; Kleiner, K.; Kunath, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1191. (f) Araki, S.; Katsumura, N.; Kawasaki, K.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 499. (g) Yi, X.-H.; Meng, Y.; Li, C.-J. *Tetrahedron Lett.* **1997**, *38*, 4731.

Scheme 2



chemistry of products was unambiguously derived from the single-crystal X-ray structure analyses of the ester derivatives.[9c] Representative X-ray structure analyses of derivatives of products unequivocally revealed the formation of *anti* isomers as the major products.

Reaction Pathway. Theoretically, an acyclic mechanism (path "a") is expected to give *anti*/*syn* isomers in the ratio of 50:50; however, the high diastereoselectivities in the present indium-based experiments undoubtedly indicate an involvement of a highly favored cyclic transition intermediate mechanism (path b). Further, the predominant formations of *anti* isomers over *syn* isomers, which was confirmed in the single-crystal X-ray structure analyses, noticeably suggest the participation of the stereochemically preferred transient *E* enolates in the transition state of the reaction pathway. Thus, the interesting reaction pathway involved in the indium-employed Reformatsky-type reactions could be predicted as shown in the Scheme 2.

^{1}H NMR Studies. We next intensively investigated the active species formed from an alkyl halide with In or indium(I) halide (Figures 1−5). An NMR tube containing an equimolar mixture of ICH_2COOEt and indium powder in THF-d_8 was subjected to ultrasonication at rt. ^{1}H NMR spectra were recorded at different intervals. Three independent singlet peaks at δ 2.08, 1.85, and 1.84 appeared (~10 min, Figure 1a). The intensity of the peak at δ 1.84 was gradually enhanced over a period of 1 h (Figure 1b, see the Supporting Information). Quenching with benzaldehyde caused an immediate disappearance of the peak at δ 1.85 (Figure 2), and the peak at δ 2.08 was also slowly consumed over 3 h. But the peak at δ 1.84 was unchanged even after 43 h. Later, this singlet peak at δ 1.84 was proved to be the methyl protons of CH_3COOEt, which could result from the active species in the presence of adventitious water.

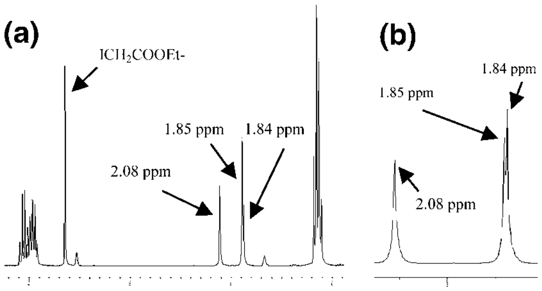


Figure 1. Partial ^{1}H NMR spectra of ICH_2COOEt-indium in THF-d_8 for (a) 10 min and (b) 60 min.

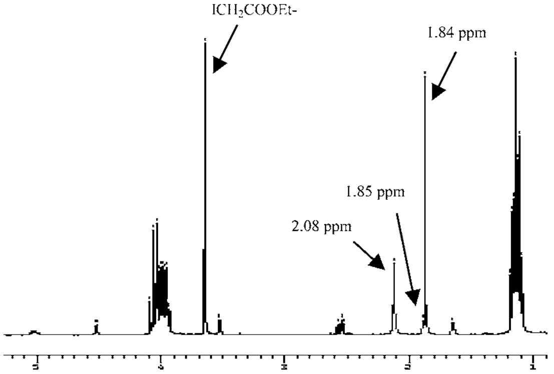


Figure 2. Partial ^{1}H NMR spectrum of ICH_2COOEt-indium in THF-d_8 for 60 min and then with benzaldehyde.

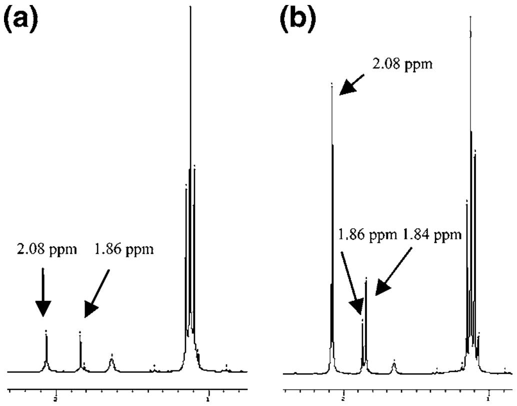


Figure 3. Partial ^{1}H NMR spectra of ICH_2COOEt with In(I)I in THF-d_8 for (a) 20 min and (b) 90 min.

Surprisingly, a similar trend was observed from an equimolar mixture of ICH_2COOEt and In(I)I in THF-d_8 (Figure 3a,b). Initially, the subsequent appearance of two

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(9) (a) With respect to yields and diastereoselection, In and InBr afforded a similar trend. But InCl and InI furnished relatively a moderate selectivity. One of the reasons might be that dissimilar halide ions react with the α-bromo ester to form the active enolates. (b) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702. (c) **Typical Experimental Procedure (Method A).** To a solution of **5c** (1 mmol) and **6a** (1.8 mmol) in dry THF (1.8 mL) was added indium powder (1.2 mmol) at room temperature. The flask was dipped into an oil bath and stirred, the bath temperature was allowed to rise until it reached 67−69 °C, and the reaction was continued for a total of 3 h. Then, the reaction mixture was cooled to room temperature. Cold water (6 mL) addition, ultrasonication (1 min), ether extraction, concentration, and repetitive column chromatography afforded both *anti*/*syn* isomers (**9a$_1$** and **9a$_2$**, respectively) in pure form. See the Supporting Information for the experimental details and the X-ray structure analyses of ester derivatives **9a$_1$B** and **13a$_1$B**, respectively, prepared from the respective alcohols **9a$_1$** and **13a$_1$** (*anti* isomers).

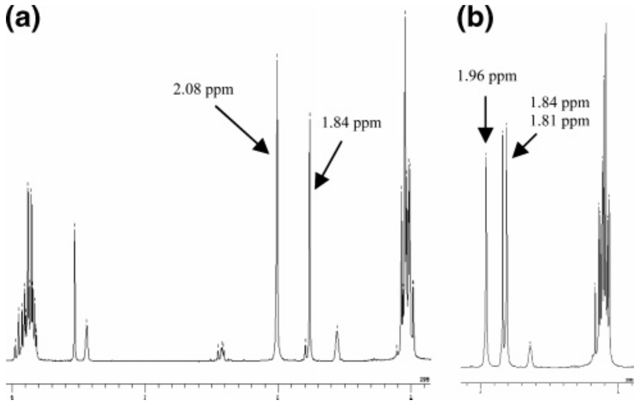

Figure 4. Partial ^{1}H NMR spectra of (a) ICH_2COOEt with In(I)I in THF-d_8 for 90 min and then with benzaldehyde and (b) $BrCH_2$-COOEt-indium in THF-d_8 for 15 min.

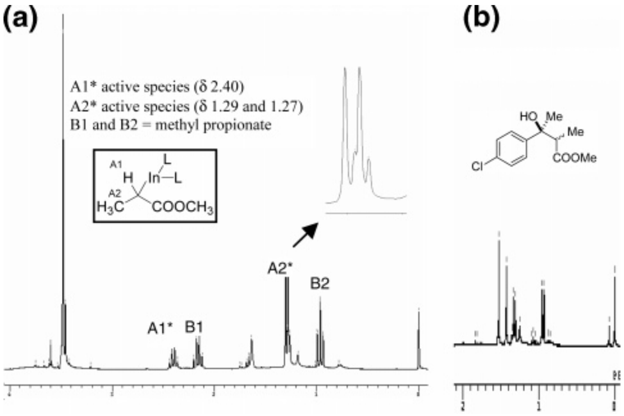

Figure 5. Partial ^{1}H NMR spectra of (a) MeCH(Br)COOMe with indium in THF-d_8, heated at 70−72 °C for 30 min, and (b) with addition of 4-chloroacetophenone.

new singlet peaks (δ 2.08 and 1.86) was observed (about 8 and 20 min). A third peak at δ 1.84 (CH_3COOEt) appeared 50 min later. Quenching with benzaldehyde caused the selective disappearance of the peak at δ 1.86 (Figure 4a). The peak at δ 2.08 was also consumed slowly. In the case of $BrCH_2COOEt$ with In, three singlet peaks at δ 1.96, 1.84, and 1.81 (∼15 min, Figure 4b) were observed, the peaks corresponding to δ 1.96 and 1.81 were found to be active, and the singlet peak at δ 1.84 was inactive and found to be the methyl protons of MeCOOEt (see the Supporting Information).

In a further experiment, a mixture of MeCH (Br)COOMe and indium in THF-d_8 was heated at 70 °C for 30 min. The ^{1}H NMR spectrum revealed the formation of two new doublet signals[11a] at δ 1.29 and 1.27 ($J = \sim 7$ Hz), corresponding to the methyl protons (Figure 5a, protons denoted as A2*) of two new active species.[10a,b] In addition, we also found the formation of methyl propionate (Figure 5a, B1 and B2). Plausibly, in the cases of MeCH (Br)COOMe and XCH_2COOEt, $MeCH_2COOMe$ and MeCOOEt, respectively, could result from the highly active species or the highly unstable indium enolate derived from an ester carbonyl group in the presence of adventitious water. Thus, this quenching of active species indicates why no Reformatsky reaction occurs in water as the solvent.[8g]

It has been envisaged that in the case of allyl halide with In or In(I)X the formation of sesquihalide-type active species[12a] ($R_3In_2X_3$) in DMF and RIn-type active species[12b] in H_2O, respectively. Our preliminary investigations on the active species involved in the case of α-halo esters with indium reagents revealed the following inferences:[11b] (a) the chemical shift values corresponding to the methylene/methane proton suggest that two independent alkyl indium species having an α-metalated structure with different oxidation states are formed; (b) one of them is very active, the real precursor of a transient indium enolate; (c) it is informative that the same kinds of transient active species are involved in both the indium metal and In(I)X systems.

Although these results may be correlated with allyl halide case,[12] we observed two kinds of active species in the case of α-halo esters with In or In(I)X under anhydrous conditions. Hence, the structures of active species with respect to the chemical shift values will be accounted for in due time.

In conclusion, we have shown that indium-based reagents exhibit a distinctive diastereoselective pattern for the Reformatsky-type reactions of ketones with the branched α-halo esters. In or In(I)X afforded the similar types of active species and reactivity trend. Demonstrations of the reaction path and groundwork investigations on the transient active species formed from the α-halo esters and indium reagents were carried out.

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Supporting Information Available: Experimental procedures, spectral data of products, ^{1}H NMR spectra, and details of X-ray structure analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) At this stage, 4-chloroacetophenone was added and the mixture heated for 30 min, which revealed the disappearances of peaks corresponding to the active species. Further usual workup and the ^{1}H NMR spectrum revealed the formation of *anti*/*syn* isomers of the respective alcohols (Figure 5b). (b) See the Supporting Information for the full ^{1}H NMR spectral region.

(11) (a) In a different experiment, when the reaction mixture was left overnight, only methyl propionate was observed. (b) In the case of InCl with ICH_2COOEt three singlet peaks at δ 1.92 (broad), 1.84 and 1.75 were observed. The singlet peak at 1.84 was inactive and accounted for CH_3 protons of MeCOOEt and the other two were found to be active. Similarly, InCl with $BrCH_2COOEt$, two singlet peaks were observed, δ 1.88 (active) and 1.84 (accounted for CH_3 protons of MeCOOEt). $InCl_2$ with $ClCH_2$-COOEt did not afford any new signal.

(12) For earlier ^{1}H NMR studies on allyl indium cases, see: (a) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228. (b) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.